Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Brain disorders: Impact of mild SARS-CoV-2 may shrink several parts of the brain

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ABSTRACT

Coronavirus (COVID-19) is a highly infectious respiratory infection discovered in Wuhan, China, in December 2019. As a result of the pandemic, several individuals have experienced life-threatening diseases, the loss of loved ones, lockdowns, isolation, an increase in unemployment, and household conflict. Moreover, COVID-19 may cause direct brain injury via encephalopathy. The long-term impacts of this virus on mental health and brain function need to be analysed by researchers in the coming years. This article aims to describe the prolonged neurological clinical consequences related to brain changes in people with mild COVID-19 infection. When compared to a control group, people those who tested positive for COVID-19 had more brain shrinkage, grey matter shrinkage, and tissue damage. The damage occurs predominantly in areas of the brain that are associated with odour, ambiguity, strokes, reduced attention, headaches, sensory abnormalities, depression, and mental abilities for few months after the first infection. Therefore, in patients after a severe clinical condition of COVID-19, a deepening of persistent neurological signs is necessary.

1. Introduction

The global pandemic caused by the SARS-CoV-2 virus has now been liable for the death of millions of people all over the world. Coronaviruses, often known as CoV, are large positive-stranded enveloped RNA viruses that generally cause respiratory diseases in humans and in animals (Gollub, 2022). SARS-CoV-2, also known as COVID-19, was discovered in Wuhan, China in December 2019 (Fischer et al., 2022). As a result of the rapid global spread of this unique coronavirus, a pandemic situation has developed, causing a severe health emergency as well as a terrible social and economic disaster. There has been a lot of emphasis focused to the long-term effects of COVID-19, which is mild to moderate in severity (Yin et al., 2022). In the first few months of the COVID-19 pandemic, doctors had a hard time keeping patients alive and focused mostly on treating damage to the lungs and circulatory system. Despite this, there was a number of studies suggesting that the drug had a negative impact on the brain. The disease's symptoms are not restricted to the respiratory system, but can affect other organs as well. In particular, neurological symptoms that are caused by viruses are being documented in the scientific literature (Zhang et al., 2022). There is a significant incidence of neurological and cognitive abnormalities in patients (Malik et al., 2022), radiographic and post-mortem tissue investigations (Raahimi et al., 2021) demonstrating the influence of COVID-19 on the brain, and the likely existence of the coronavirus (Davis et al., 2021). These are only some of the researches that have proven that the COVID-19 virus has a direct effect on the brain. Fig. 1 describes the N protein, on the other hand, interacts with the viral RNA into the core of the virion (capsid-encapsulated viruses with DNA or RNA molecules).

1.1. Does virus invade the brain?

This SARS-CoV-2 has been demonstrated to penetrate the olfactory mucosa (Lemprière, 2021 Feb), which can result in a loss of smell. It is possible that the virus enters the brain by the vagal or trigeminal pathways; however, there has not been any evidence that can definitely support this claim. An unstable Blood-Brain Barrier (BBB) may allow SARS-CoV-2 to enter and spread throughout the brain (Santos et al., 2020 Aug 13). Circumventricular Organs (CVOs), situated halfway between the third and fourth ventricles, may monitor blood and cerebrospinal fluid levels by employing fenestrated capillaries devoid of blood-brain barrier junctional proteins. Viral RNA was detected using reverse transcription-quantitative real-time polymerase chain reaction in the medulla and cerebellum (Daniels et al., 2014), both of which are

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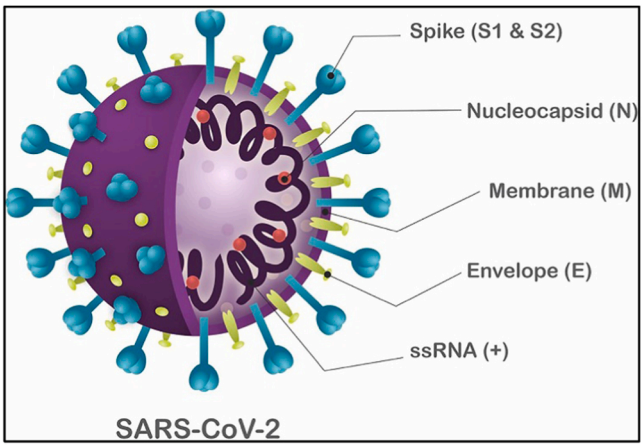

Fig. 1. SARS-CoV2 Structure.
Figure adapted from (Santos et al., 2020 Aug 13).

proximal to the region postrema, a CVO crucial for mediating emetic reactions to poisons. In spite of this, the SARS-CoV-2 protein was only detected in the vascular endothelium of the brain, and not in neurons or glia (Liu et al., 2021). The blood supply may have contaminated the lesions and Virchow-Robin gaps where viral RNA was detected.

Neutrophil phagocytosis (neuronophagia) and microglial nodules (neuronophagia) were shown to be related with a sparse lymphocytic infiltration in the brain stem and less commonly in cortical and limbic areas in a human histopathologic examination (Al-Dalahmah et al., 2020). CVO and brain stem virus invasion may cause ageusia, nausea, and vomiting, although neuroinflammation and hypoxic damage are more likely to cause short-term and long-term Neuropeptide (NP) effects. There is a possibility that the brain stem is involved in the ongoing autonomic dysfunction and anxiety.

After the initial symptoms of COVID have subsided, many patients experience persistent brain fog, drowsiness, and issues with attention and memory. This condition, sometimes known as 'long COVID,' can persist for months after a mild infection has occurred (Littlejohns et al., 2020). More than half of those who have COVID, even if they have a moderate illness, will develop long COVID (Douaud et al., 2022). This data was acquired by scientists as a part of a massive UK Biobank database (Douaud et al., 2022). MRI scans and tests of brain function performed on 785 volunteers before to the pandemic were examined by the researchers (Gollub, 2022). A three-year period later, they looked at the same data and found that half of the subjects had moderate COVID infection while the other half did not (Gollub, 2022). Therefore, scientists were able to identify the consequences of mild COVID infection on brain anatomy and function.

A. The thickness of the grey matter and the diminution of tissue contrast in the orbitofrontal cortex and the para hippocampal gyrus

   The orbitofrontal cortex is the area of the brain that regulates pleasure, emotion, and mood swings, as well as feelings of sorrow. It's also a part of thinking and making decisions (Fischer et al., 2022). The Para hippocampal gyrus has a crucial function in memory recall, spatial awareness and processing as well as in controlling our emotions. A COVID infection can cause sadness, anxiety, and "brain fog," which can lead to memory problems in those who have been infected.

B. Damage to tissues in areas that work with the primary olfactory cortex.

   Olfactory cortex is the brain region responsible for smell processing and perception; it also aids in the association of smells to specific memories and survival reactions (Wang et al., 2020). This may provide some light on why one of the most prominent symptoms of COVID-19 is a loss of ability to smell.

C. Greater reduction in global brain size

After being infected with COVID, participants' brains were found to be smaller than they were before they were infected. Researchers estimate that we lose 0.2–0.3% of our grey matter per year as we get older, which is typical for the normal ageing process (Yin et al., 2022). When compared to uninfected individuals, the study discovered that all participants who infected COVID, no matter how minor their symptoms, lost anywhere from 0.2% to 2.0% in their olfactory cortex during scans and had disrupted connections between different brain regions (Huang, 2022).

2. Related work

The UK Biobank is a large biological repository and research platform that collects data on the genetic structure and health of half a million individuals across the country (www.ukbiobank.ac.uk). A total of 100,000 people has had or will have an MRI scan. The biobank began a COVID-19 repeat-imaging study in the year 2020 (for further details, please see (go.nature.com/3gvj6qe). For the purposes of this study, individuals who had finished their medical imaging treatment prior to the outbreak of the pandemic were requested to undergo an identical second scan session (Littlejohns et al., 2020). Approximately 785 'before and after' scan images have been submitted by the UK biobank. Participants in this study ranged in age from 51 to 81. In the UK biobank, it is found that whereas 384 individuals tested negative for COVID-19 between appointments, 401 patients tested positive. There were no known variants affected, although the scans were done before the Omicron variation appeared. The authors (Douaud et al., 2022) analysed scans obtained before and during the pandemic to distinguish between the effects of the virus and those caused by pre-existing disorders. Another group of people who had long-term brain scans in a biobank before the outbreak (Alfaro-Almagro et al., 2018) was included as a comparison group. Unlike well-established medical tests, such as those used to detect blood glucose levels, the standards for gathering and analysing complicated brain imaging data are in a continual state of evolution.

There are six different types of MRI images in the UK Biobank neuroimaging session (Gollub, 2022). Imaging-Derived Phenotypes (IDPs) are the characters that are taken from the images by an automated process. Each individual IDP communicates a distinct piece of information, such as the volume or the microstructural tissue qualities of various brain areas or the strength of neuronal connections between two distinct regions of the cerebral cortex. During a scan session, IDPs are generated for each person. The collection of IDPs (Douaud et al., 2022) to investigate the hypothesis that COVID-19 causes impairments in the ability to perceive tastes, odours, and textures by the brain. This work uses computational models from a prior biobank imaging study to examine the impact of COVID-19 infection on brain structure and function (Miller et al., 2016). Those who tested positive for SARS-CoV-2 (the case group) were markedly different from those who did not (the control group). Compared to the control group, the case group showed thinner cortical layers and less tissue contrast in certain regions of the brain (see Fig. 2). This is a common indicator of declining brain health. In addition, there were more indicators of tissue damage in regions of the brain that are associated with smell and taste in the case group.

No difference was seen between the principal olfactory pathways of the two groups, which is to be anticipated given that these are notoriously difficult locations for MRI due to imaging errors at air–tissue interfaces. These findings were validated by whole-brain scans, which revealed widespread atrophy across the brain. In (Douaud et al., 2022) were identified these brain changes because most of the people in the case group had mild to moderate COVID-19 signs.

2.1. Coronavirus - induced neurological symptoms

Brain damage caused by COVID-19 was initially identified by (Mao

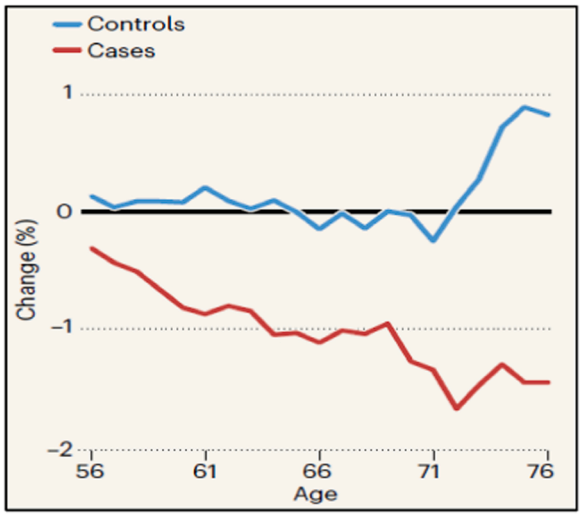

Fig. 2. A reduction in cortex thickness after COVID-19.
Figure adapted from (Gollub, 2022).

et al., 2020). SARS-CoV-2 was found in 214 patients at hospitals in Wuhan, China. Injury to peripheral nerves, central nervous system problems, and skeletal muscle damage are all on the list of possible neurological abnormalities. Finally, 78 people (36.4% of the sample) had neurological symptoms, with 53 of those (24.8%) originating in the central nervous system. Dizziness (16.8%) and headache (13.1%) were the most frequently reported neurological symptoms, affecting 28 out of the 102 patients. Ageusia 12 (5.6%) and anosmia 11 (5.6%) were among the symptoms reported. Patients with skeletal muscle injury were found in 11.7%. Neurologic symptoms such as decreased eyesight and skeletal muscle damage, as well as an excessive level of C-reactive protein in the plasma, were more common in patients with severe infections (Alfaro-Almagro et al., 2021). Neurological symptoms included mood oscillations, exhaustion and headaches, altered vision, myalgia, poor mobility and memory loss as well as tremors and anosmia in 68.33% of COVID-19 patients were seen in research (Helms et al., 2020). The majority of patients (over 50%) still had neurological problems three months after their recovery. COVID-19 infection has been linked to a variety of neurological complications, including encephalitis, micro- and haemorrhage, encephalopathy, and cerebral venous embolism (Qin et al., 2020).

2.2. *Coronavirus-associated psychiatric symptoms*

Numerous research has been conducted to examine the effect of COVID-19 on a person's mental health. Psychiatric symptoms might arise due to an infection in the CNS or the immune system (Wang et al., 2020). The development of mental disorders may also be influenced by additional social pressures, which have been shown to increase the prevalence and severity of mental illnesses.

Recent research (Malik et al., 2022; Han et al., 2021) has demonstrated that the membrane protein neuropilin-1, which is abundantly expressed in neurons, is a factor that facilitates the entry of SARS-CoV-2 into the cells of the nervous system. The symptoms of encephalopathy can vary greatly in terms of severity, from a mild headache to serious psychological impairment, delirium, or dementia (Xie et al., 2021). SARS-CoV-2 can cause encephalopathy, and it is more common in the elderly and those with pre-existing chronic conditions. Individuals who already had cognitive decline or dementia, for instance, might exhibit a worsening of these illnesses as a result of the treatment.

3. Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2)

SARS-CoV-2 and SARS-CoV share 79.5% of their genome, and it is similar up to 96% of its genome with bat coronavirus (Davies et al., 2020). Patients infected with SARSCoV-2 can have fever or a mild cough to pneumonia and major problems with a number of organs, which can lead to death in 2–4% of cases. The current clinical data reveals that some individuals with COVID-19 have symptoms similar to those of intracranial infections, such as headache, seizures, and altered consciousness. An increasing number of people with COVID-19 are losing their sense of smell or taste without noticing it. As a direct consequence of this, persons affected by COVID-19 may exhibit symptoms of anosmia and dysgeusia. COVID-19-related symptoms may not even appear in some patients until they have experienced neurological problems (Varatharaj et al., 2021). An encephalitis case caused by a new CoV that attacked the central nervous system was recently reported by Beijing Ditan Hospital (Wu et al., 2020) for the first time. Genome sequencing showed the presence of SARS-CoV-2 in cerebral fluid, supporting the idea that this novel pneumonia virus might potentially cause neurological injury (Miller et al., 2016). In individuals with severe COVID-19 symptoms, the Blood-Brain Barrier (BBB) may be destroyed by other pathogenic microorganisms, such as bacteria, resulting in secondary intracranial infections that can cause headaches, projectile vomiting, vision or cognitive impairment and limb convulsions.

Damage to the hippocampus and cingulate gyrus can cause anosmia as well as memory loss (Siano et al., 2020). This brain region is responsible for a wide range of emotional and cognitive activities, including anxiety and depression. These conditions are conveyed to other parts of the brain via the hippocampus (HPC) and prefrontal cortex (PFC) pathway. Severe depression, anxiety, Alzheimer's disease, and schizophrenia can all be caused (Moriguchi et al., 2020) when the pathway is injured or impaired. Using the data in Table 1, researchers can better understand how COVID-19 damages the brain's nerves and how it affects the patient's recovery from COVID-19-related encephalopathy. Fig. 3 depicts the recovery of the nervous system microstructure from COVID-19 encephalopathy from December 2019 to December 2021.

3.1. *Long COVID risk and protective factor*

Since only people who got tested for COVID-19 were included in the study and not everyone who was at risk for COVID-19, the study may have been affected by selection bias. This problem is of particular relevance given the large incidence of mild infections (illnesses that do not require medical treatment) (Lu et al., 2020) or asymptomatic infections3, as well as the fact that access to testing was extremely limited during the time period of the study (Ruggiero et al., 2021; Freeman et al., 2021; Qin et al., 2021). Because COVID-19 testing may be prompted by factors other than infection and symptoms (e.g., comorbidities, health consciousness, access to healthcare), it is possible that both the outcome of interest (having COVID-19) and the exposure (influenza vaccination) contributed to the inclusion of these individuals in the analytic sample (e.g., health-seeking behaviour, health consciousness, comorbidities). A misleading, skewed negative connection may occur even if the null association is true (Hellgren et al., 2021) if the common effect being conditioned on (in this case, COVID-19 testing) is positively associated with both the exposure and the result.

3.2. *Measuring and significance of statistical methods*

The statistical approaches available for assessing the significance of a trend or a set of trends are diverse. Much exploratory research has been conducted on COVID-19, and the results provide a framework for future trend analysis. The authors (Lemprière, 2021 Feb) employed Pearson correlation to analyse the time series of Google searches for newly

Table 1
Changes in brain microstructure after three, six, and twelve months after rehabilitation.

Period of symptoms	Imaging technique	Patients Brain imaging features	References
3 months	Brain MR Image	White matter lesions that are extension confluent or multifocal, as well as micro-haemorrhages, diffusion restriction, and enhancement.	(Freeman et al., 2021)
3 months	Brain MR Image	The left insula lobe, hippocampus, and superior temporal gyrus were shown to have thinner cortical layers than their right-side counterparts.	(Qin et al., 2021)
3 months	Brain MR image	Several areas of the brain are susceptible to white matter injuries, including the frontoparietal lobes, the grey matter junction, and others.	(Hellgren et al., 2021)
6 months	^{18}F-FDG-PET	There were several cases of hypometabolic prefrontal cortex, but no severe pathogenic changes were seen.	(Guedj et al., 2021)
7 months	Brain, MRI, DWI	A chronic hypersignal in the brain's white matter is characteristic of cystic leuko encephalomalacia, as are multi-modal cystic lesions seen in different regions of the brain white matter.	(Lang et al., 2021)
9 months	Brain MR Image	There were no abnormalities seen in the olfactory brain, bulb, or sulcus.	(Cecchini et al., 2022)
1 year	Brain MR Image	The 3-month follow-up MRI demonstrated T2/FLAIR hyperintensity in white matter in the parietal and occipital brain, associated with vision impairment. Symptoms and indicators persist a year later.	(Hixon et al., 2022)

reported cases of COVID-19. To account for incubation durations, the authors (Xie et al., 2021; Siano et al., 2020; Hellgren et al., 2021) assessed correlations between search counts and the new case metric at varying time lags. Searches and cases were found to have no correlation on day 7 (P = 0.178), but a considerable correlation on day 12 (r = 0.978, P 0.001) and day 19 (r = 0.973, P 0.001). Acute infection rates were compared over time using Spearman correlation trend tests, which revealed statistically significant differences between 2004 and 2014 (P 0.001) (Davies et al., 2020). It has also been suggested that Spearman's correlation be used to identify linear patterns over time, especially in exploratory research (Varatharaj et al., 2021). As an extension of this application of the Spearman correlation, it was found that the Fisher's z-transformation could be used to provide a strong comparison between two Spearman's rho values, just as with Pearson values. Treatment of Spearman as Pearson values was found to be more effective in avoiding Type I errors than alternatives such as ignoring normality assumptions (Wu et al., 2020), as determined by researchers using Monte Carlo simulations.

There is broad consensus that the Spearman correlation is a good statistical test for trends in time series, but the literature also suggests that the Mann-Kendall (M-K) tests may be more appropriate for some applications. The null hypothesis (H0) for M-K tests is that the distributions of the two datasets which are similar, whereas the alternative (Ha) is a monotonic trend (Siano et al., 2020; Moriguchi et al., 2020; Lu et al., 2020). The Seasonal Kendall (S-K) test (Ruggiero et al., 2021) is an extension of the M-K test that can be utilized if one is concerned about "seasonality" impacts on trends. Calendar seasons aren't the only things that can be "seasonal" (e.g., spring, summer). Days, months, and quarters are only a few examples, but it can apply to any time frame where change is possible on a regular basis. With the S-K test, you may rule out the possibility of a monotonic trend (H0) by comparing it to the alternative (Ha), which states that a monotonic trend does exist (for at least one of the "seasons") (Freeman et al., 2021).

Recent research on COVID-19 cases and prevalence has made use of two additional analyses to find trends. Daily effective reproductive numbers (R) have been trended using Dickey-Fuller (D-F) tests (Yin et al., 2022). In addition to the D-F test, the literature on time series analysis describes an enhanced version of the test called the Augmented DF (ADF) test. It's more capable of handling complex data (Qin et al., 2021). Data stationarity (where variance and mean do not change over time) is assumed in the ADF test, while non-stationarity (H0) is tested against this assumption. In a nutshell, these analyses look for evidence of stationarity and the causes of any observed variations, such as seasonality or an actual trend (Hellgren et al., 2021). In conclusion, recent literature has described the value of Mann-Whitney U tests in evaluating

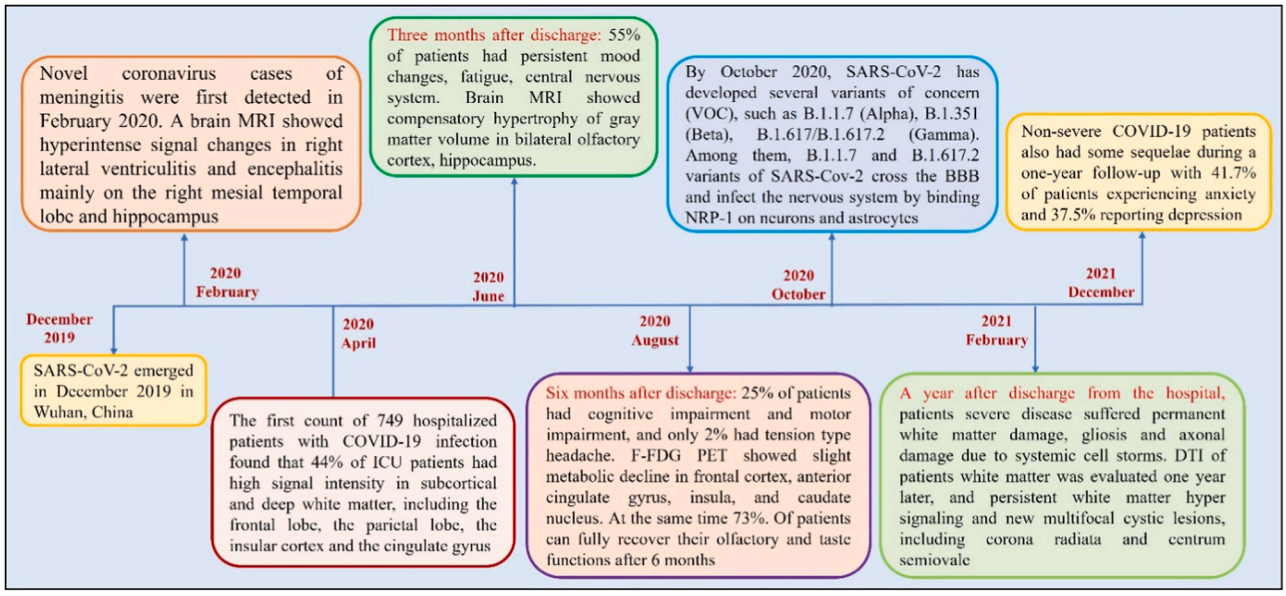

Fig. 3. Represents the dynamic clinical timeline and dynamics of microstructural changes in Coronavirus Disease-19 (COVID-19) encephalopathy. Figure adapted from (Huang, 2022).

time-series data using the Monte Carlo method. Using this method, researchers were able to separate out periods of time that did not overlap.

4. Brain imaging findings for long COVID-19 or post-COVID-19 individuals

Long COVID was characterised by the presence of at least one persistent symptom for a period of at least three months following the onset of symptoms, hospitalisation, or diagnosis (Lu et al., 2020) (See Table 1). The term "long COVID" refers to symptoms that last for at least two months after being discharged from the hospital, whereas chronic COVID-19 symptoms can last for weeks before being discharged. Rehabilitation has an immense role to bring back the achievable functional status of COVID-19 patients (Ostrowska et al., 2023). Long-term COVID symptoms, related risk factors, and treatment options are shown in Fig. 4.

4.1. Brain imaging findings at 3 months of rehabilitation

After three months of rehabilitation, twenty percent of the patients suffered headaches, sixty percent of the patients had coughs, forty-three percent of the patients had increased expectoration, sixty-seven percent of the patients experienced active chest tightness and palpitations, and fifty percent of the patients were exhausted all the time. The lungs of 82% of patients who underwent a second High-Resolution Computed Tomography (HRCT) assessment were found to be normal. Extrapulmonary causes may have caused chronic harm in the majority of individuals following infection (Ruggiero et al., 2021). After a recent follow-up of 804 patients in two Italian hospitals who had been treated for COVID-19 virus, two patients were readmitted to the hospital due to acute ischemic stroke despite no sign of infection recurrence (Mumoli et al., 2020). This result was confirmed as a basis of findings the study that followed up on 804 people who had been cured from COVID-19 virus. The white matter of the brain of 59 patients with COVID-19 had abnormal, T2 signalling and decreased diffusion, according to a study of their brain MRIs. Disseminated leukoencephalopathy (DLE) has been related to COVID-19. Neurocognitive functioning and leukoencephalopathy were correlated using brain MRI imaging changes four months after discharge. Imaging revealed that 25 patients had white matter lesions in the subcortical frontal and parietal lobes, accounting for 71% of the cases. It was found that memory problems and cognitive impairment were present in 16 individuals (46% of the group). It was detected in the brains of severely impaired or old persons who had chronic cognitive impairment and sustained unfavourable outcomes (Freeman et al., 2021). In a follow-up investigation of critically sick patients who also had associated delirium, hyperintensity on T2/FLAIR scans was detected in the anterior, posterior, and frontal lobes of the brain as well as microbleeds in the corpus callosum. The patient's visual cognitive abilities were tested after they were released from the hospital by utilising a standardised icon known as the Family Confusion Assessment Method (FAM-CAM). According to research published in the Journal of Neurology (Hellgren et al., 2021), delayed delirium and cognitive impairment may have been brought on by a neuroinflammatory response to COVID-19.

MRI of the brain revealed haemorrhages in the subcortical space, the basal ganglia, and the cerebellum, as well as elevated T2/FLAIR signals in the white matter of a patient with COVID-19-related diffuse leukoencephalopathy. However, three months after being in a severe condition, the patient regained consciousness and was able to walk alone. The prognosis of individuals with leukodystrophy or cerebral microhaemorrhage can be improved with early intervention treatment (Ragheb et al., 2021). There was an uncommon microhaemorrhage in

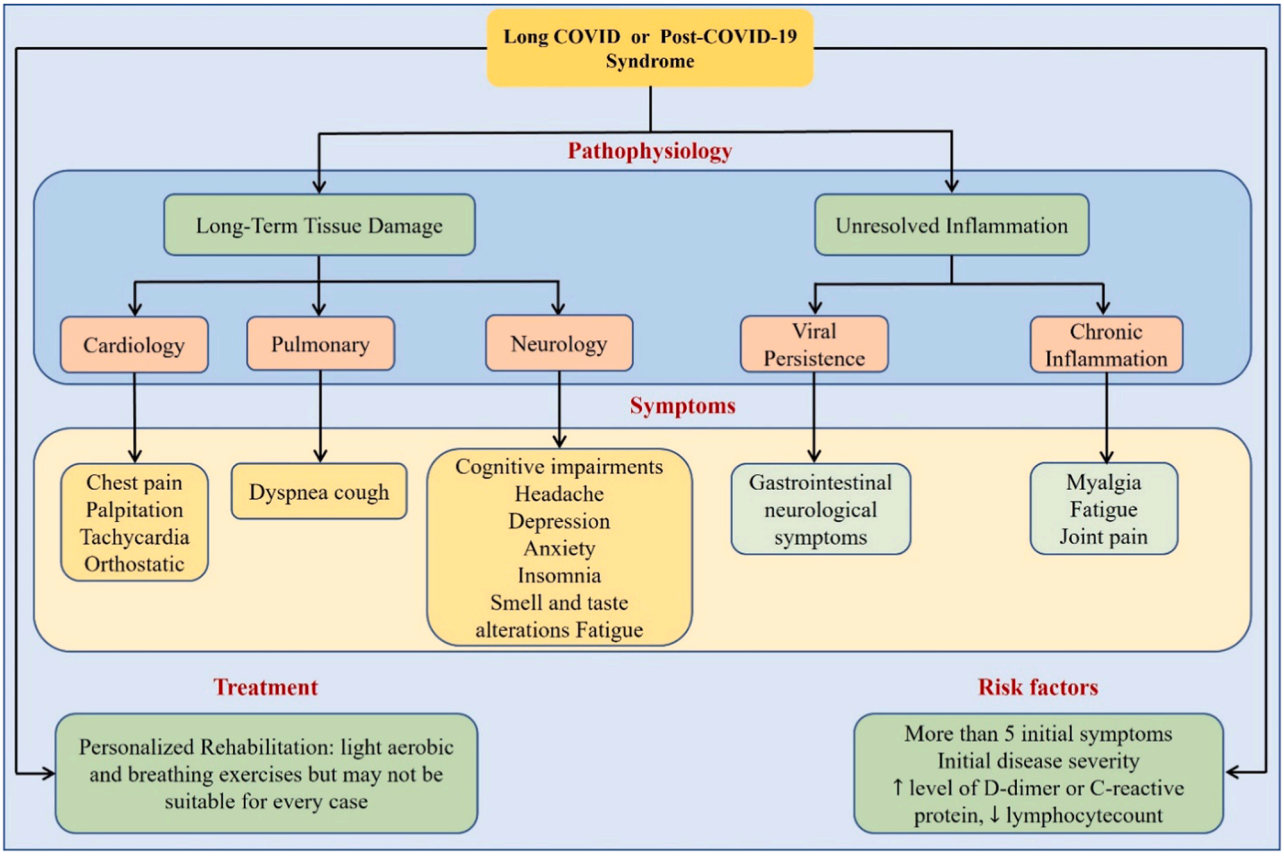

Fig. 4. An overview of the symptoms, putative pathophysiology, associated risk factors, and potential treatments involved in long COVID. Figure adapted from (Yong, 2021)

the white matter of the cerebral lobes, as well as an abnormality in the cerebrospinal fluid (CSF) called albumin cytologic dissociation, which was identified by brain MRI. Since the patient was able to walk again two months after receiving antiviral, immunoglobulin therapy, and rehabilitation therapy, it is recommended that early detection and early treatment be followed for COVID-19-related encephalopathy (Kanberg et al., 2021; Huang, 2022).

A regular MRI scan of the patient's brain was taken three months after they were released from the hospital, allowing researchers to determine whether or not there is a correlation between the degree of sickness during the acute phase of COVID-19 infection and the degree to which the brain's microstructure is transformed. The severity of left insula lobe, hippocampus, and superior temporal gyrus cortical thickness was correlated with smaller cluster sizes ($p < 0.05$), higher serum inflammatory marker (procalcitonin (PCT)) levels, and smaller hippocampal volume ($p < 0.05$) compared to healthy controls. In patients with severe illness, a cytokine storm during the early stages of illness elicits a robust stress response in the brain. Both the bilateral superior medial frontal gyrus and the left insula of severe patients showed significant decreases in Cerebral Blood Flow (CBF) values.

4.2. Brain imaging findings after 6 months of rehabilitation

It has been observed that the effects of COVID-19 can endure for at least six months, with post-intensive care syndrome (PICS) frequently occurring in patients who are seriously infected. At six months, 76% still reported feeling fatigued, weak, or sleepy, and 23% of those patients also reported feeling depressed or anxious. Because of the distinctive physiology of women and the more severe nature of their illnesses, women were found to be more susceptible to the development of long-term problems related to their mental health. More female patients than male patients reported feeling nervous and sad following COVID-19 (Yong, 2021). It was revealed that women who had been diagnosed with COVID-19 and had been discharged from the hospital for three months had a typical hair loss sequela. This was thought to be the result of the inflammatory response induced by COVID-19 or the mental state of patients during the illness. Recovering from a serious illness can have a significant influence on a patient's quality of life and cognitive performance when anxiety and sadness are present.

Glial fibrillary acidic protein (GFAP) and neurofilament light polypeptide (NFL) plasma levels both increased after SARS-CoV-2 infection of the central nervous system. Symptoms of brain damage include the protein GFAP. It is fair to assume that systemic inflammation induces white matter nerve damage because of the connection between injured regions on plain computed tomography images and the serum protein GFAP (Mahammedi et al., 2021). Multiple studies that took blood samples from patients in the acute phase and again six months later found an association between the severity of illness and the concentration of biomarkers of Central Nervous System (CNS) damage in the blood. Growth differentiation factor 15 (GDF-15) and glial fibrillary acidic protein (GFAP) levels in the blood were substantially higher ($p < 0.05$) in patients who were critically ill. As neuroinflammation reduced over the course of six months, plasma levels of NFL and GFAP reverted to normal, and the GDF-15 concentration dropped. After six months, neuronal axonal damage has been healed and astrocyte levels have gradually returned to normal, demonstrating that serum biomarkers may be utilised as a prognosis to evaluate COVID-19. Higher concentrations of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6) were identified in COVID-19 patients who also reported pain from tension-type headaches. Six months after recovery, the percentage of those who experienced tension headaches reduced from 38% to 2% (Mayi et al., 2021; Huang, 2022).

In order to understand the remission of COVID-19 patients' symptoms, long-term follow-up must be paired with pathophysiology. The majority of infected patients recover their olfactory and gustatory capabilities within two weeks, and 66% of patients are able to regain these functions completely within six months, according to recent prospective research (McMahon et al., 2015). Parosmia is a particular sign of infection in patients. Additionally, research indicated that female patients were more susceptible to SARS-CoV-2 infection because of their susceptibility to both olfactory and gustatory abnormalities, with 20% of patients still experiencing these symptoms seven months later (Douaud et al., 2022). Patients suffering from anosmia, olfactory abnormalities, and taste problems were shown to have Angiotensin-Converting Enzyme 2 (ACE2) expression in their nasal nerves over a period of 15 months (Meinhardt et al., 2021). Pan-Cytokeratin (PCK) antibodies were used to confirm the presence of SARS-CoV-2 virus in the CNS. A nine-month follow-up MRI of the brain's olfactory blubs and cortex revealed no structural changes or abnormally high signal characteristics. After 9 months, the patient's olfactory bulb lesions appeared to be improving (Xiong et al., 2020). When ACE2 levels are high in the prefrontal cortex and amygdala, it is linked to mood and mental illness. This is because the RAS system has already been demonstrated to modulate the Ang-(1−7) pathway in such regions. Inflammatory mediators, such as IL-6 and CRP, can be successfully reduced by ACE inhibitors, which can have a role in reducing depression, anxiety, and other negative feelings.

4.3. Brain imaging findings at 1 year of rehabilitation

In the first three months of recovery, a patient's neurological system should be showing signs of improvement, therefore investigations after a year are essential. This study followed 2433 patients for a year after they were discharged from Wuhan Hospital to see how they were doing. Chronic fatigue, sweating, anxiety, and joint pain were all still reported by critically ill patients throughout evaluation; cerebrovascular disease was a strong predictor of CNS impairment (De Moraes De Medeiros et al., 2021). Another study found that after a year of follow-up, 41.7% of those with mild COVID-19 experienced anxiety and 37.5% experienced depression. Patients' anxiety and sadness subsided as they recovered from the condition, and their cortisol levels reduced as a result.

When comparing the images of patients with mild and severe COVID-19, early results show that patients recovered after one year. For the purpose of determining whether changes in brain microstructure caused by COVID-19 persist, assisting clinicians in understanding the potential neurological damage caused by the drug, and providing data to support clinical intervention for patients with neurological damage after recovery, a longitudinal comprehensive evaluation of abnormal changes in brain imaging was carried out. White matter illness, which has a fundamental impact on cognition and behaviour, should be the focus of our efforts. One of the pathological indications of patient recovery is the restoration of Diffusion Tensor Imaging (DTI) of subcortical white matter to normal levels, which can be attributed to ageing and the loss of white matter integrity. COVID-19 patients' chronic nervous systems changed following white matter damage. Axial fractional anisotropy (FA) suggested an isolated impairment of white matter pathways, and acute MRI of the brain showed very little diffusion of white matter in the bilateral deep brain. After 7 months of treatment, an MRI scan of the brain showed persistent white matter hypersignal and new multifocal cystic lesions in areas including the centrum semiovale and Creatine (CR). Axonal injury, gliosis, and hypoxia may have contributed to white matter damage (DeKosky et al., 2020). Brain lesions in COVID-19 individuals were symmetrical, with significant bleeding in white matter and the knee of the corpus callosum. The patient was diagnosed with acute haemorrhagic leukoencephalopathy after several magnetic resonance imaging scans. Acute widespread encephalomyelitis may be diagnosed by using magnetic resonance imaging (MRI) to detect the progressive atrophy of white matter that underlies lesions in the frontoparietal lobe of the brain. In this way, convalescent-stage detection of acute haemorrhagic white matter encephalitis was made possible (Ermis et al., 2020). Patients who have had persistent neurological symptoms for a long time are at increased risk for mental health issues and

structural abnormalities in the brain due to their exposure to COVID-19. The most recent study of 4828 patients with post-Intensive care syndrome (PICS) indicated that 37.5% of those affected by PICS also suffered from anxiety and that 20% of those affected also suffered from post-traumatic stress disorder (PTSD). After a year, researchers in another study (Fischer et al., 2022; Ostrowska et al., 2023) found that 38.3% of ICU patients had developed mental health symptoms, demonstrating the need of paying attention to mental health problems. Furthermore, an unusual finding: in both intensive care unit (ICU) and general ward patients, the severity of the patient's illness was not significantly connected with the persistence of psychological symptoms such as worry, pain, and sadness throughout follow-up were observed (Zhang et al., 2022; Huang, 2022).

4.4. Statistical analysis

The pooled prevalence was estimated by random-effects meta-analyses using MetaXL software and the double arcsine transformation (Lopez-Leon et al., 2022). The estimated prevalence (in percentage form) includes 95% confidence intervals (CIs). Long-COVID cases were counted as the numerator, and all cases of acute COVID-19 were counted as the denominator (with and without long-term effects). Review Manager (RevMan) software 5.4 is used to estimate odds ratios (O.R.s) (O'Driscoll et al., 2021 Jul 1) by comparing cases and controls after controlling for potential confounders. If the p-value was less than 0.05, it was regarded to be significant. A random-effects model was used with the I^2 statistic due to the anticipated heterogeneity. In meta-analysis, the fraction of variance that is due to heterogeneity is estimated by the statistic I^2. Heterogeneity was classified as low, medium, or high depending on whether I^2 was 25, 50, or 75%. Studies with higher precision are shown closer to the middle, and those with lower precision are sped up on both ends of the distribution. Publication bias may be indicated by a deviation from a normal-looking funnel distribution. Using the QCed data, the study's quality assurance procedures were evaluated. This index measures the quality of studies assessing prevalence, and it is described and recommended in the MetaXL Guidelines (Lopez-Leon et al., 2022). More than 40 chronic clinical symptoms have been linked to COVID-19, as shown in Table 2.

Studies included in the meta-analyses found that certain variables, such as age, sex, severe acute-COVID-19, obesity, allergic disease, and long-term health conditions increased the risk of long-COVID.

5. Conclusion and future scope

There are several symptoms that can be caused by a systemic immune response, such as acute viral encephalitis, which can lead to white matter lesions and anosmia as well as cerebrovascular illness and mental symptoms such as sadness and anxiety. More than a year has passed since the first case of COVID-19 was recorded, on December 31, 2019. Long-term health surveillance is needed for COVID-19-infected patients. At least two weeks following SARS-CoV-2 virus infection, microangiopathy was observed in the brain using CT or MRI. ^{18}F-FDG-PET was used widely to track progress following COVID-19. The 1-year follow-up study found that the frontal lobes of the brain were the most affected by decreased brain metabolism.

5.1. Importance of defining long COVID

The information at hand points to Long COVID as a significant public health issue with serious ramifications for those afflicted and society at large. Psychological distress is frequently reported by patients with Long COVID. In the United States, people with acute or chronic COVID-19 have reported moderate to severe monetary impacts (Halder et al., 2022; Muthusami and Saritha, 2020 Jun). The fact that patients with Long COVID have a higher rate of impairment due to shortness of breath and a lower quality of life is a concern (Proal and VanElzakker, 2021; Davis et al., 2023). In order to help these patients, recover, we need to know what they require in terms of healthcare, rehabilitation, and other resources (Ison, 2020 Sep-Oct). Therefore, establishing a research infrastructure that precisely examines the natural history of this

Table 2
Pooled prevalence of symptoms in individuals (Lopez-Leon et al., 2022).

Clinical manifestations	Studies	Cases	Sample size	I^2	Prevalence % (95% CI)
Mood (sad, tense, angry, depression, anxiety)	6	720	6037	97.9	16.0 (7.7–28.1)
Fatigue	17	3025	21,392	99.2	9.6 (4.4–16.6)
Sleep disorder (insomnia, hypersomnia, poor sleep quality)	9	163	1532	93.9	8.4 (3.4–15.0)
Headache	12	1855	21,208	98.9	7.8 (4.0–12.0)
Respiratory symptoms	8	1337	19,113	99.5	7.6 (2.0–15.8)
Sputum/nasal congestion	3	13	152	0	7.5 (3.7–12.6)
Cognition (less concentration, learning difficulties, confusion, memory loss)	10	1213	19,203	91.1	6.2 (4.4–8.3)
Loss of appetite	6	746	9339	93.4	6.0 (3.9–8.5)
Exercise intolerance	3	7	151	87.7	5.7 (0.0–19.8)
Altered smell (hyposmia, anosmia, hypersomnia, parosmia, phantom smell)	11	2038	20,318	97.1	5.6 (3.1–8.6)
Hyperhidrosis	3	46	734	93.9	4.6 (0.0–13.5)
Chest pain	7	457	18,277	98.4	4.6 (1.5–9.1)
Dizziness	7	781	9341	97.7	4.4 (1.5–8.5)
Rhinorrhea	4	55	1134	94.0	4.1 (0.1–11.9)
Cough	11	520	18,688	86.0	3.8 (2.6–5.19)
Myalgia/arthralgia	8	537	18,564	93.7	3.7 (2.1–5.7)
Body weight changes	4	40	875	96.2	3.9 (0.0–14.00)
Altered taste	6	1263	15,005	92.3	3.6 (1.3–6.2)
Otalgia (tinnitus, earache, vertigo)	2	217	3673	92.5	3.4 (0.8–7.5)
Ophthalmologic (conjuntivitis, dry eye, problems seeing/ blurred vision, photophobia, pain)	5	334	9311	91.7	3.0 (1.6–4.9)
Abdominal pain	7	267	9311	73.4	2.9 (2.0–3.2)
Dermatologic (dry skin, itchy skin, rashes, hives)	5	228	9222	78.8	2.6 (1.7–3.7)
Sore throat	3	411	11,311	98.6	2.4 (0.2–6.3)
Chest tightness	8	283	6419	92.1	2.4 (0.5–5.5)
Variations in heart rate	3	28	719	88.4	2.2 (0.0–7.6)
Constipation	2	30	1001	81.1	2.0 (0.3–4.5)
Dysphonia	5	52	3201	2	1.8 (1.4–2.8)
Fever	4	157	17,709	96.7	1.8 (0.5–3.9)
Musculoskeletal other	8	373	14,618	87.2	1.7 (0.4–3.8)
Diarrhea	6	228	18,337	81.1	1.6 (0.6–3.8)
Vomiting/nausea	8	250	14,144	24.1	1.5 (1.0–2.3)
Changes in menstruation	5	13	856	43.8	1.2 (0.3–2.0)
Palpitations	6	155	6278	93.5	1.2 (0.0–3.3)
Hair loss	4	15	1309	80.1	1.1 (0.1–3.0)
Neurological abnormalities (pins and needles, tremor, numbness)	3	4	947	0	0.8 (0.3–1.5)
Urinary symptoms	2	7	1160	0	0.6 (0.2–1.1)
Dysphagia	5	6	1207	0	0.4 (0.1–0.3)
Speech disturbances	6	4	1197	40.1	0.4 (0.0–1.0)

condition is crucial to determining patient needs. It is likely that therapeutic care should be individualised for patients with extended clinical symptoms following acute COVID-19 due to the diversity in their clinical appearances. However, without evidence-based guidelines, clinical management of Long COVID remains difficult. In addition, existing studies frequently offer aggregated results for patients with varying clinical histories, such as those with severe COVID requiring admission to an ICU and those with mild COVID requiring hospitalisation but not ICU care. The existing literature provides conflicting accounts of Long COVID's evolutionary origin. One study (Han et al., 2021) indicated that chronic fatigue does not depend on the severity of the initial illness, while another (Hellgren et al., 2021) found that 26 out of 65 (40%) people with mild COVID also experienced chronic fatigue. However, there is a lack of information about the prevalence of long-term effects in the general community; the published research have only examined COVID-19 individuals who sought medical assistance.

5.2. COVID-19 and quality of life

Infection with SARS-CoV-2 and the subsequent pandemic are both expected to have serious consequences for patients' health. Specifically, mental health, nutrition, and physical fitness may be affected by the larger societal response to SARS-CoV-2. The World Health Organization issued guidelines early in the epidemic to aid with mental health care (Mental health and psychosocial considerations during the COVID-19 outbreak). Since then, numerous reports have raised alarm about a worldwide increase in psychological and emotional suffering (Rando et al., 2021; Borch et al., 2022). Although COVID-19 patients, and especially those with more severe cases, are likely to experience unique psychological stressors, it may be challenging to identify the impact of a societal decline in psychological health (including addiction/substance abuse disorder) in studies that evaluate only COVID-19 patients with and without Long COVID. Similarly, viral infections can worsen pain and other chronic conditions (Roge, 2021), however it may appear that these effects are unique to SARS-CoV-2 depending on the study design. In a similar vein, the pandemic conditions have diminished the availability of healthy food options (Smane et al., 2021; Asadi-Pooya et al., 2021 Oct) and physical activity (Buonsenso, 2021). Patients with substance use disorders have additional difficulties when they are isolated from others, as feelings of isolation and stress might increase their propensity to use drugs or alcohol (Blankenburg, 2022). Long COVID patients' reports of their quality of life and psychosocial well-being may change in conjunction with the population at large as a result of the government's and society's responses to SARS-CoV-2.

5.3. Neuroimaging in analyses of long COVID

Several neuroimaging findings in COVID-19 patients have been documented, and research is ongoing to determine their pathophysiologic causes and neuroanatomical connections. Several investigations, such as (Erol et al; Fink), have been conducted to describe the neuroimaging findings and associated neuropsychiatric symptoms of COVID-19. A small number of imaging investigations have attempted to establish neuroimaging correlates with specific symptoms; for example, an MR imaging study of COVID-19 anosmia patients identified abnormalities in the olfactory bulb (Littlejohns et al., 2020). Symptoms of hyposmia and anosmia, memory and cognitive impairment, pain, and insomnia were all linked to clusters of hypometabolism in the olfactory gyrus, right temporal lobe (including the hippocampus and amygdala), bilateral pons/medulla brainstem, and bilateral cerebellum in a study comparing 35 Long COVID patients to 44 controls (Knoke et al., 2022). According to recent reports (Fischer et al., 2022; Zhang et al., 2022; Malik et al., 2022; Davis et al., 2021; Jong, 2021) several clinical indications of COVID-19 have been linked to brainstem dysfunction. For instance, (Rando et al., 2021) cites a number of autopsy studies to support this hypothesis.

In future we recommend ^{18}F-FDG-PET (Guedj et al., 2021) be utilised for lifelong patient monitoring in clinical follow-up. On top of that, it will reveal the pathophysiological process of post-COVID-19, as well as metabolic anomalies in many organs of the body. Vaccination and antiviral medication therapy are now the major therapeutic treatments for COVID-19 [80]. This work conclude that the mildest post-COVID-19 symptoms could be relieved within six months, but ICU patients were more likely to have long-term consequences. Post-COVID-19 individuals may be at risk for developing neurological diseases, and this finding will help neurosurgeons and radiologists better understand the pathophysiology of post-COVID-19.

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Conflict of interest

The authors declare no competing interests.

Data Availability

Data will be made available on request.

References

Al-Dalahmah, O., Thakur, K.T., Nordvig, A.S., et al., 2020. Neuronophagia and microglial nodules in a SARS-CoV-2 patient with cerebellar hemorrhage. Acta Neuropathol. Commun. 8 (1), 147. https://doi.org/10.1186/s40478-020-01024-2.

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L.R., Griffanti, L., Douaud, G., et al., 2018. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage vol 166, 400–424. https://doi.org/10.1016/j.neuroimage.2017.10.034.

Alfaro-Almagro, Fidel, McCarthy, Paul, Afyouni, Soroosh, Andersson, Jesper L.R., Bastiani, Matteo, Miller, Karla L., Nichols, Thomas E., Smith, Stephen M., 2021. Confound modelling in UK Biobank brain imaging. NeuroImage Volume 224 (117002). https://doi.org/10.1016/j.neuroimage.2020.117002.

Asadi-Pooya, A.A., Nemati, H., Shahisavandi, M., Akbari, A., Emami, A., Lotfi, M., Rostamihosseinkhani, M., Barzegar, Z., Kabiri, M., Zeraatpisheh, Z., Farjoud-Kouhanjani, M., Jafari, A., Sasannia, F., Ashrafi, S., Nazeri, M., Nasiri, S., 2021. Long COVID in children and adolescents. World J. Pedia 17 (5), 495–499. https://doi.org/10.1007/s12519-021-00457-6.

Blankenburg, J., et al., 2022. Comparison of mental health outcomes in seropositive and seronegative adolescents during the COVID19 pandemic. Sci. Rep. 12, 2246. https://doi.org/10.1038/s41598-022-06166-y.

Borch, L., Holm, M., Knudsen, M., Ellermann-Eriksen, S., Hagstroem, S., 2022. Long COVID symptoms and duration in SARS-CoV-2 positive children—a nationwide cohort study. Eur. J. Pedia 181, 1597–1607. https://doi.org/10.1007/s00431-021-04345-z.

Buonsenso, D., et al., 2021. Preliminary evidence on long COVID in children. Acta Paediatr. 110, 2208–2211. https://doi.org/10.1111/apa.15870.

Cecchini, M.P., Brozzetti, L., Cardobi, N., Sacchetto, L., Gibellini, D., Montemezzi, S., et al., 2022. Persistent chemosensory dysfunction in a young patient with mild COVID-19 with partial recovery 15 months after the onset. Neurol. Sci. vol.43, 99–104. https://doi.org/10.1007/s10072-021-05635-y.

Daniels, B.P., Holman, D.W., Cruz-Orengo, L., Jujjavarapu, H., Durrant, D.M., Klein, R.S., 2014. Viral pathogen-associated molecular patterns regulate blood-brain barrier integrity via competing innate cytokine signals. no. e01476-e14 mBio Vol. 5 (5). https://doi.org/10.1128/mBio.01476-14. no. e01476-e14.

Davies, J., Randeva, H.S., Chatha, K., Hall, M., Spandidos, D.A., Karteris, E., Kyrou, I., 2020. Neuropilin-1 as a new potential SARS-CoV-2 infection mediator implicated in the neurologic features and central nervous system involvement of COVID-19. Mol. Med Rep. vol.22 (issue.5), 4221–4226. https://doi.org/10.3892/mmr.2020.11510.

Davis, H.E., Assaf, G.S., McCorkell, L., Wei, H., Low, R.J., Re'em, Y., Redfield, S., Austin, J.P., Akrami, A., 2021. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine vol.38 (101019). https://doi.org/10.1016/j.eclinm.2021.101019.

Davis, H.E., McCorkell, L., Vogel, J.M., Topol, Eric J., 2023. Long COVID: major findings, mechanisms and recommendations. Nat. Rev. Microbiol 21, 133–146. https://doi.org/10.1038/s41579-022-00846-2.

De Moraes De Medeiros, S., Vandresen, R., Gomes, E., Mazzuco, E., 2021. Mental health and quality of life in COVID-19 survivors: a needed discussion. J. Intern. Med. 744–745. https://doi.org/10.1111/joim.13342.

DeKosky, S.T., Kochanek, P.M., Valadka, A.B., Clark, R.S.B., Chou, S.H., Au, A.K., et al., 2020. Blood biomarkers for detection of brain injury in COVID-19 patients. J. Neurotrauma vol.38, 1–43. https://doi.org/10.1089/neu.2020.7332.

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., et al., 2022. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature vol 604 (7907), 697–707. https://doi.org/10.1038/s41586-022-04569-5.

Ermis, U., Rust, M.I., Bungenberg, J., Costa, A., Dreher, M., Balfanz, P., et al., 2020. Neurological symptoms in COVID-19: a cross-sectional monocentric study of hospitalized patients. Neurol. Res. Pract. Vol.3 (17) https://doi.org/10.1186/s42466-021-00116-1.

Erol, N., Alpinar, A., Erol, C., Sari, E. & Alkan, K. Intriguing new faces of Covid-19: Persisting clinical symptoms and cardiac effects in children, Cardiology in the Young, 32(7), 1085–1091. ⟨doi:10.1017/S1047951121003693⟩.

Fink, T.T. et al. Persistent symptoms and decreased health-related quality of life after symptomatic pediatric COVID-19: A prospective study in a Latin American tertiary hospital. Clinics (Sao Paulo) 76, e3511. ⟨https://doi.org/10.6061/clinics/2021/e3511⟩.

Fischer, D., Snider, S.B., Barra, M.E., Sanders, W.R., Rapalino, O., Schaefer, P., Foulkes, A.S., Bodien, Y.G., Edlow, B.L., 2022. Disorders of consciousness associated with COVID-19 a prospective multimodal study of recovery and brain connectivity. no. e315-e325 Neurology vol. 98 (3). https://doi.org/10.1212/WNL.0000000000013067. no. e315-e325.

Freeman, C.W., Masur, J., Hassankhani, A., Wolf, R.L., Levine, J.M., Mohan, S., 2021. Coronavirus disease (COVID-19)-related disseminated leukoencephalopathy: a retrospective study of findings on brain MRI. Am. J. Roentgenol. Vol.216, 1046–1047. ⟨https://www.ajronline.org/doi/10.2214/AJR.20.24364⟩.

Freeman, C.W., Masur, J., Hassankhani, A., Wolf, R.L., Levine, J.M., Mohan, S., 2021. Coronavirus disease (COVID-19)-related disseminated leukoencephalopathy: a retrospective study of findings on brain MRI. Am. J. Roentgenol. vol.216, 1046–1047. ⟨https://www.ajronline.org/doi/10.2214/AJR.20.24364⟩.

Gollub, Randy L., 2022. Brain changes after COVID revealed by imaging. Nature no. 604, 633–634. https://doi.org/10.1038/d41586-022-00503-x.

Guedj, E., Campion, J.Y., Dudouet, P., Kaphan, E., Bregeon, F., Tissot-Dupont, H., et al., 2021. 18)F-FDG brain PET hypometabolism in patients with long COVID. Eur. J. Nucl. Med. Mol. Imaging 48, 2823–2833. https://doi.org/10.1007/s00259-021-05215-4. ⟨https://doi.org/10.1007/s00259-021-05215-4⟩.

Halder, B., Bandyopadhyay, J., Banik, P., 2022. Statistical data analysis of risk factor associated with mortality rate by COVID-19 pandemic in India. Model Earth Syst. Environ. 8 (1), 511–521. https://doi.org/10.1007/s40808-021-01118-3. ⟨https://doi.org/10.1007/s40808-021-01118-3⟩.

Han, Y., Yuan, K., Wang, Z., et al., 2021. Neuropsychiatric manifestations of COVID-19, potential neurotropic mechanisms, and therapeutic interventions. Transl. Psychiatry vol.11 (499). https://doi.org/10.1038/s41398-021-01629-8.

Hellgren, L., Birberg Thornberg, U., Samuelsson, K., Levi, R., Divanoglou, A., Blystad, I., 2021. Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalisation: an observational cohort study. BMJ Open vol.11 (e055164). https://doi.org/10.1136/bmjopen-2021-055164.

Hellgren, L., Birberg Thornberg, U., Samuelsson, K., Levi, R., Divanoglou, A., Blystad, I., 2021. Brain MRI and neuropsychological findings at long-term follow-up after COVID-19 hospitalisation: an observational cohort study. BMJ Open vol.11 (e055164). https://doi.org/10.1136/bmjopen-2021-055164.

Helms, J., Kremer, S., Merdji, H., et al., 2020. Neurologic features in severe SARS-CoV-2 infection. N. Engl. J. Med. vol.382, 2268–2270. https://doi.org/10.1056/NEJMc2008597.

Hixon, A.M., Thaker, A.A., Pelak, V.S., 2022. Persistent visual dysfunction following posterior reversible encephalopathy syndrome due to COVID-19: case series and literature review. Eur. J. Neurol. Vol.28, 3289–3302. https://doi.org/10.1111/ene.14965.

Huang, Yan, et al., 2022. Brain imaging changes in patients recovered from COVID-19: a narrative review. Front. Neurosci. vol. 16 https://doi.org/10.3389/fnins.2022.855868.

Ison, D., 2020 -. Statistical procedures for evaluating trends in coronavirus disease-19 cases in the United States. Int J. Health Sci. 14 (5), 23–31. ⟨https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7475210/⟩.

Jong, Shin Jie, 2021. Persistent brainstem dysfunction in long-COVID: a hypothesis. ACS Chem. Neurosci. 12 (4), 573–580. https://doi.org/10.1021/acschemneuro.0c00793.

Kanberg, N., Simrén, J., Edén, A., Andersson, L.M., Nilsson, S., Ashton, N.J., et al., 2021. Neurochemical signs of astrocytic and neuronal injury in acute COVID-19 normalizes during long-term follow-up. EBioMedicine vol.70 (103512). https://doi.org/10.1016/j.ebiom.2021.103512.

Knoke, L.S.A., Maier, C., Eitner, L., Lücke, T., Brinkmann, F., 2022. Pulmonary function and long-term respiratory symptoms in children and adolescents after COVID-19. Front. Pedia vol. 10. https://doi.org/10.3389/fped.2022.851008.

Lang, M., Chang, Y.S., Mehan Jr., W.A., Rincon, S.P., Buch, K., 2021. Longterm neuroimaging follow-up of COVID-19-related leukoencephalopathy. Neuroradiology vol. 63, 2153–2156. https://doi.org/10.1007/s00234-021-02829-1.

Lemprière, S., 2021. SARS-CoV-2 detected in olfactory neurons. Nat. Rev. Neurol. 17 (2), 63. https://doi.org/10.1038/s41582-020-00449-6.

Littlejohns, T.J., Holliday, J., Gibson, L.M., Garratt, S., Oesingmann, N., et al., 2020. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. no. 2624 Nat. Commun. vol. 11 (1). https://doi.org/10.1038/s41467-020-15948-9. no. 2624.

Liu, J.M., Tan, B.H., Wu, S., Gui, Y., Suo, J.L., Li, Y.C., 2021. Evidence of central nervous system infection and neuroinvasive routes, as well as neurological involvement, in the lethality of SARS-CoV-2 infection. J. Med Virol. 93 (3), 1304–1313. https://doi.org/10.1002/jmv.26570.

Lopez-Leon, S., Wegman-Ostrosky, T., Ayuzo Del Valle, N.C., Perelman, C., Sepulveda, R., Rebolledo, P.A., Cuapio, A., Villapol, S., 2022. Long-COVID in children and adolescents: a systematic review and meta-analyses. Sci. Rep. 12, 9950. https://doi.org/10.1038/s41598-022-13495-5.

Lu, Y., Li, X., Geng, D., Mei, N., Wu, P.Y., Huang, C.C., et al., 2020. Cerebral micro-structural changes in COVID-19 patients - an MRI-based 3-month follow-up study. E-Clin. Med. vol.25 (100484) https://doi.org/10.1016/j.eclinm.2020.100484.

Mahammedi, A., Saba, L., Vagal, A., Leali, M., Rossi, A., Gaskill, M., et al., 2021. Imaging of neurologic disease in hospitalized patients with COVID-19: an italian multicenter retrospective observational study. Radiology vol.297, E270–E273. https://doi.org/10.1148/radiol.2020201933.

Malik, P., Patel, K., Pinto, C., Jaiswal, R., Tirupathi, R., Pillai, S., et al., 2022. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-a systematic review and meta-analysis. J. Med. Virol. Vol. 94, 253–262. ⟨https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.27309⟩.

Mao, L., Jin, H., Wang, M., et al., 2020. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. vol.77, 683–690. https://doi.org/10.1001/jamaneurol.2020.1127.

Mayi, B.S., Leibowitz, J.A., Woods, A.T., Ammon, K.A., Liu, A.E., Raja, A., 2021. The role of neuropilin-1 in COVID-19. PLoS Pathog. Vol.17 (e1009153) https://doi.org/10.3390/biomedicines10082032.

McMahon, P.J., Panczykowski, D.M., Yue, J.K., Puccio, A.M., Inoue, T., Sorani, M.D., et al., 2015. Measurement of the glial fibrillary acidic protein and its breakdown products GFAP-BDP biomarker for the detection of traumatic brain injury compared to computed tomography and magnetic resonance imaging. J. Neurotrauma vol.32, 527–533. https://doi.org/10.1089/neu.2014.3635.

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., et al., 2021. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat. Neurosci. vol.24, 168–175. https://doi.org/10.1038/s41593-020-00758-5.

Miller, K.L., Alfaro-Almagro, F., Bangerter, N.K., Thomas, D.L., et al., 2016. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat. Neurosci. vol.19 (issue.11), 1523–1536. https://doi.org/10.1038/nn.4393.

Moriguchi, T., Harii, N., Goto, J., et al., 2020. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J. Infect. Dis. vol.94, 55–58. https://doi.org/10.1016/j.ijid.2020.03.062.

Mumoli, N., Vitale, J., Mazzone, A., 2020. Clinical immunity in discharged medical patients with COVID-19. Int. J. Infect. Dis. Vol. 99, 229–230. https://doi.org/10.1016/j.ijid.2020.07.065.

Muthusami, R., Saritha, K., 2020. Statistical analysis and visualization of the potential cases of pandemic coronavirus. Virusdisease 31 (2), 204–208. https://doi.org/10.1007/s13337-020-00610-1.

O'Driscoll, M., Harry, C., Donnelly, C.A., Cori, A., Dorigatti, I., 2021. A comparative analysis of statistical methods to estimate the reproduction number in emerging epidemics, with implications for the current coronavirus disease 2019 (COVID-19) pandemic. Clin. Infect. Dis. 73 (1), e215–e223. https://doi.org/10.1093/cid/ciaa1599.

Ostrowska, M., Rzepka-Cholasińska, A., Pietrzykowski, Ł., Michalski, P., Kosobucka-Ozdoba, A., Jasiewicz, M., Kasprzak, M., Kryś, J., Kubica, A., 2023. Effects of multidisciplinary rehabilitation program in patients with long COVID-19: post-COVID-19 rehabilitation (PCR SIRIO 8) study. J. Clin. Med. 12, 420. https://doi.org/10.3390/jcm12020420.

Proal, Amy, VanElzakker, Michael, 2021. Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. Front. Microbiol. vol. 12 https://doi.org/10.3389/fmicb.2021.698169.

Qin, C., Zhou, L., Hu, Z., et al., 2020. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin. Infect. Dis. vol.71, 762–768. https://doi.org/10.1093/cid/ciaa248.

Qin, Y., Wu, J., Chen, T., Li, J., Zhang, G., Wu, D., et al., 2021. Long-term microstructure and cerebral blood flow changes in patients recovered from COVID-19 without neurological manifestations. J. Clin. Invest. Vol.131 (e147329). ⟨https://www.jci.org/articles/view/147329⟩.

Raahimi, M.M., Kane, A., Moore, C.E., Alareed, A.W., 2021. Late onset of Guillain-Barre syndrome following SARS-CoV-2 infection: part of 'long COVID-19 syndrome. no. e240178 BMJ Case Rep. vol. 14 (1). https://doi.org/10.1136/bcr-2020-240178. no. e240178.

Ragheb, J., McKinney, A., Zierau, M., Brooks, J., Hill-Caruthers, M., Iskander, M., et al., 2021. Delirium and neuropsychological outcomes in critically Ill patients with COVID-19: a cohort study. BMJ Open vol.11 (e050045). https://doi.org/10.1136/bmjopen-2021-050045.

Rando H.M., Bennett T.D., Byrd J.B., Bramante C., Callahan T.J., Chute C.G., Davis H.E., Deer R., Gagnier J., Koraishy F.M., Liu F., McMurry J.A., Moffitt R.A., Pfaff E.R., Reese J.T., Relevo R., Robinson P.N., Saltz J.H., Solomonides A., Sule A., Topaloglu U., Haendel M.A. Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. medRxiv [Preprint]. 2021 Mar 26:2021.03.20.21253896. ⟨https://doi.org/10.1101/2021.03.20.21253896⟩.

Roge, I., et al., 2021. Comparison of persistent symptoms after COVID-19 and other non-SARS-CoV-2 infections in children. Front. Pediatr. 9, 752385 https://doi.org/10.3389/fped.2021.752385.

Ruggiero, R.N., Rossignoli, M.T., Marques, D.B., de Sousa, B.M., Romcy-Pereira, R.N., Lopes-Aguiar, C., et al., 2021. Neuromodulation of hippocampalprefrontal cortical synaptic plasticity and functional connectivity: implications for neuropsychiatric disorders. Front. Cell Neurosci. vol.15 (732360) https://doi.org/10.3389/fncel.2021.732360.

Santos, I.A., Grosche, V.R., Bergamini, F.R.G., Sabino-Silva, R., Jardim, A.C.G., 2020. Antivirals against coronaviruses: candidate drugs for SARS-CoV-2 treatment? Front. Microbiol 11, 1818. https://doi.org/10.3389/fmicb.2020.01818.

Siano, M., Oreni, L., Rusconi, S., Gervasoni, C., Ridolfo, A.L., Rizzardini, G., Antinori, S., Galli, M., 2020. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. Clin. Infect. Dis. vol.71 (issue.15), 889–890. https://doi.org/10.1093/cid/ciaa330.

Smane, L., Roge, I., Pucuka, Z., Pavare, J., 2021. Clinical features of pediatric post-acute COVID-19: a descriptive retrospective followup study. Ital. J. Pediatr. 47, 177. https://doi.org/10.1186/s13052-021-01127-z.

Varatharaj, A., Thomas, N., Ellul, M.A., Davies, N., Pollak, T.A., Tenorio, E.L., et al., 2021. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry Vol.7, 875–882. https://doi.org/10.1016/S2215-0366(20)30287-X.

Wang, D., Hu, B., Hu, C., et al., 2020. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. J. Am. Med Assoc. vol.323, 1061–1069. https://doi.org/10.1001/jama.2020.1585.

Wu, Yeshun, Xu, Xiaolin, Chen, Zijun, Duan, Jiahao, Hashimoto, Kenji, Yang, Ling, Liu, Cunming, Yang, Chun, 2020. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav. Immun. Volume 87, 18–22. https://doi.org/10.1016/j.bbi.2020.03.031.

Xie, Q., Liu, X.B., Xu, Y.M., et al., 2021. Understanding the psychiatric symptoms of COVID-19: a meta-analysis of studies assessing psychiatric symptoms in Chinese patients with and survivors of COVID-19 and SARS by using the Symptom Checklist-90-Revised. Transl. Psychiatry vol. 11 (290). https://doi.org/10.1038/s41398-021-01416-5.

Xiong, Q., Xu, M., Li, J., Liu, Y., Zhang, J., Xu, Y., et al., 2020. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. Clin. Microbiol. Infect. Vol.27, 89–95. https://doi.org/10.1016/j.cmi.2020.09.023.

Yin, J., Li, C., Ye, C., Ruan, Z., Liang, Y., Li, Y., et al., 2022. "Advances in the development of therapeutic strategies against COVID-19 and perspectives in the drug design for emerging SARS-CoV-2 variant,". Comput. Struct. Biotechnol. J. vol.20, 824–837. https://doi.org/10.1016/j.csbj.2022.01.026.

Yong, S.J., 2021. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect. Dis. 53 (10), 737–754. https://doi.org/10.1080/23744235.2021.1924397.

Zhang, R., Lai, J., Wang, Y., Huang, J., Hu, S., Wang, H., 2022. Mental health outcome and resilience among aiding Wuhan nurses: one year after the COVID-19 outbreak in China. J. Affect. Disord. Vol.297, 348–352. https://doi.org/10.1016/j.jad.2021.10.050.